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Original Research

Obicetrapib plus ezetimibe as an adjunct to high-intensity statin therapy: A randomized phase 2 trial

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KEYWORDS
Obicetrapib;
Cholesteryl ester transfer protein;
Ezetimibe;
High-intensity statin;
Dyslipidemia;
Low-density lipoprotein cholesterol

Background: Obicetrapib, a selective cholesteryl ester transfer protein (CETP) inhibitor, reduces low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), lipoprotein particles, and apolipoproteins, when added to high-intensity statin in patients with dyslipidemia.

Objective: To evaluate the safety and lipid-altering efficacy of obicetrapib plus ezetimibe combination therapy as an adjunct to high-intensity statin therapy.

Methods: This double-blind, randomized, phase 2 trial administered 10 mg obicetrapib plus 10 mg ezetimibe ($n = 40$), 10 mg obicetrapib ($n = 39$), or placebo ($n = 40$) for 12 weeks to patients with LDL-C >70 mg/dL and triglycerides (TG) <400 mg/dL, on stable high-intensity statin. Endpoints included concentrations of lipids, apolipoproteins, lipoprotein particles, and proprotein convertase subtilisin kexin type 9 (PCSK9), safety, and tolerability.

Results: Ninety-seven patients were included in the primary analysis (mean age 62.6 years, 63.9% male, 84.5% white, average body mass index of 30.9 kg/m^2). LDL-C decreased from baseline to week 12 by 63.4%, 43.5%, and 6.35% in combination, monotherapy, and placebo groups, respectively ($p<0.0001$ vs. placebo). LDL-C levels of <100, <70, and <55 mg/dL were achieved by 100%, 93.5%, and 87.1%, respectively, of patients taking the combination. Both active treatments also significantly re-

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duced concentrations of non-HDL-C, apolipoprotein B, and total and small LDL particles. Obicetrapib was well tolerated and no safety issues were identified.

Conclusion: The combination of obicetrapib plus ezetimibe significantly lowered atherogenic lipid and lipoprotein parameters, and was safe and well tolerated when administered on top of high-intensity statin to patients with elevated LDL-C.

Introduction

Multiple lines of evidence demonstrate that elevated levels of atherogenic lipoproteins are a major risk factor for atherosclerotic cardiovascular disease (ASCVD) and their reduction is a cornerstone of ASCVD prevention.[1-4] A log-linear relationship between absolute low-density lipoprotein cholesterol (LDL-C) and ASCVD risk is supported by genomic and cohort studies, and randomized clinical trials.[1] A meta-analysis of 21 clinical trials of LDL-C–lowering drugs indicated that each 1-mmol/L LDL-C lowering was associated with a relative reduction in risk of major vascular events of 23% after 5 years, with increasing benefit observed with greater duration of treatment.[5]

While statins are the first-choice pharmacological agent for patients with elevated LDL-C levels, observational studies consistently demonstrate that their use in clinical practice is suboptimal. These studies demonstrate only half of patients with ASCVD are treated with a statin and only 20% of patients receive a high-intensity statin.[6, 7] As a consequence, the majority of high-risk patients with ASCVD fail to achieve guideline-mandated LDL-C treatment goals.[7-9] These studies not only demonstrate suboptimal use of high-intensity statin therapy, but also demonstrate that very few patients are treated with combination lipid-lowering therapy.[7-9] In a similar fashion to the increasing use of combination therapies required to achieve optimal control of blood pressure and glucose, increasing evidence suggests that the use of additional lipid-lowering agents will be required in combination with intensive statin therapy to achieve low LDL-C levels.[2, 10]

Obicetrapib is an oral cholesteryl ester transfer protein (CETP) inhibitor currently in clinical development for the treatment of hypercholesterolemia and reduction of cardiovascular risk.[11-13] Early studies of obicetrapib have shown it to reduce LDL-C by up 50% and be well tolerated, when administered as monotherapy in combination with both moderate- and high-intensity statins.[12, 13] The objective of the Study to Evaluate the Effect of Obicetrapib in Combination with Ezetimibe as an Adjunct to High Intensity Statin Therapy (ROSE2) was to evaluate the lipid efficacy of the combination of obicetrapib and ezetimibe in patients whose LDL-C was suboptimally controlled despite use of high-intensity statins.

Methods

This is a placebo-controlled, double-blind, randomized, phase 2 trial of obicetrapib as monotherapy and in combination with ezetimibe (NCT05266586). The trial was conducted from March 2022 to September 2022 at 18 clinical research sites in the US. The protocol was approved by Advarra Institutional Review Board (Columbia, MD), and all participants provided informed consent before their enrollment.

Participants

Participants included men and women 18–75 years of age with a fasting LDL-C >70 mg/dL and triglycerides (TG) <400 mg/dL, while receiving a stable dose of high-intensity statin therapy (atorvastatin 40–80 mg or rosuvastatin 20–40 mg) for at least 8 weeks prior to screening. Exclusion criteria were current clinically manifest ASCVD including, but not limited to, a major adverse cardiovascular event (defined as cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or non-elective coronary revascularization) within 3 months prior to randomization or New York Heart Association Functional Classification Class III or IV heart failure, concomitant use of proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors or bempedoic acid, body mass index ≥40 kg/m^2, glycated hemoglobin ≥10%, uncontrolled hypertension, active muscle disease or persistent creatine kinase >3 times the upper limit of normal (ULN), renal dysfunction (estimated glomerular filtration rate <60 mL/min), hepatic dysfunction (liver enzymes >2 times ULN or total bilirubin >1.5 times ULN), significant anemia, and recent history of malignancy or alcohol or drug abuse.

Study visits

Participants were randomized, using an automated interactive response technology system, in a 1:1:1 ratio to the following treatment groups: placebo (one placebo tablet plus one placebo capsule), obicetrapib monotherapy (one 10 mg obicetrapib tablet plus one placebo capsule), or combination therapy (one 10 mg obicetrapib tablet plus one 10 mg ezetimibe capsule). Randomization was stratified according to screening LDL-C level of ≥100 or <100 mg/dL. Following

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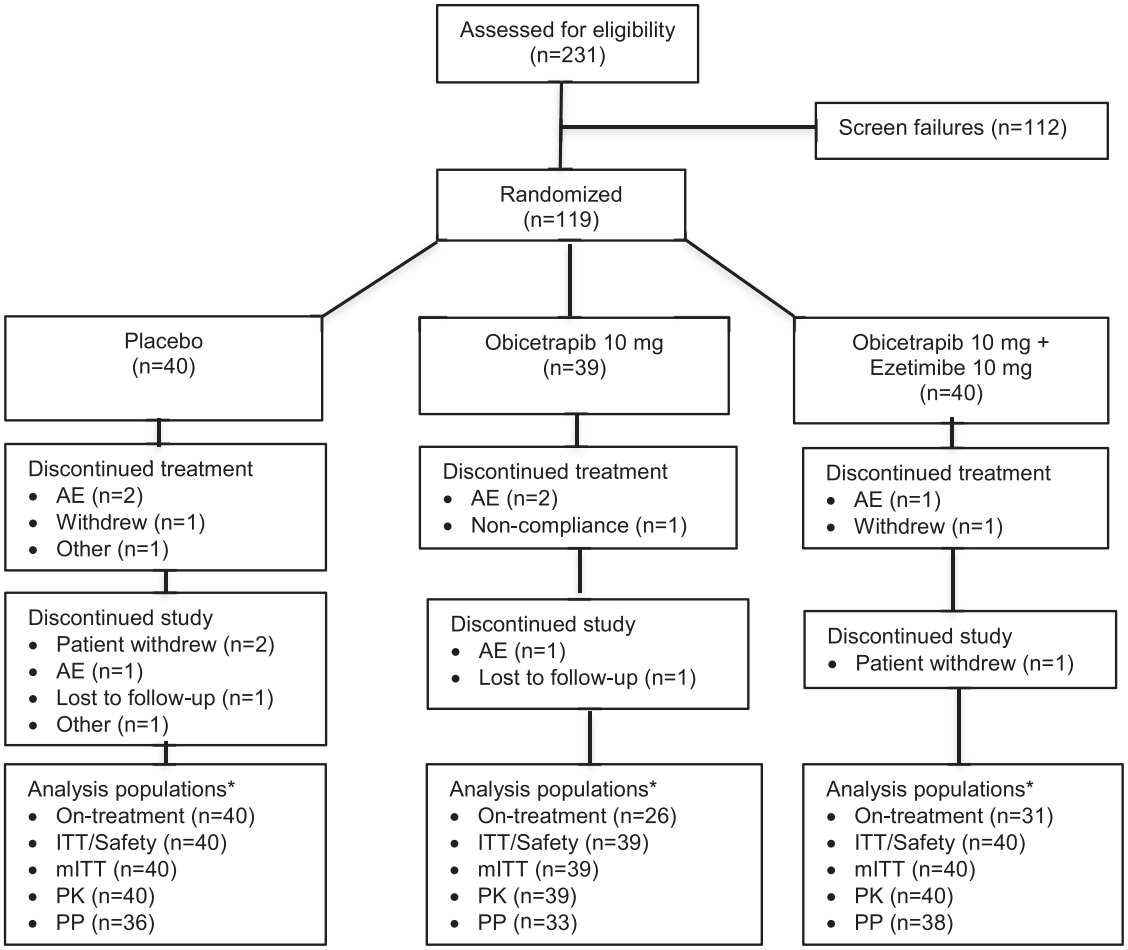

Figure 1 Participant flowchart. *On-treatment defined as participants in the mITT population excluding those with PK evidence suggesting participant misconduct, i.e., plasma obicetrapib <100 ng/mL; ITT defined as all randomized participants; safety defined as all participants who received at least one dose of any study drug; mITT defined as all participants in the ITT population who received at least 1 dose of any study drug and had a baseline value for low-density lipoprotein cholesterol (LDL-C); PK defined as all participants in the mITT population who had sufficient blood samples collected for valid estimation of obicetrapib concentration; PP defined as all participants in mITT population who had week 12 value for LDL-C and did not have a major protocol deviation that potentially impacted the primary efficacy endpoint Abbreviations: AE, adverse event; ITT, intent to treat; mITT, modified intent to treat; PK, pharmacokinetic; PP, per protocol.

randomization, participants were seen at the clinic at week 4, end of treatment at week 12, and at a final visit 4 weeks following cessation of treatment for assessment of safety and a pharmacokinetic (PK) evaluation. During the 12-week treatment period, participants were instructed to take the study drugs orally once daily with water at approximately the same time each morning. Participants were instructed to bring all their study drug supply to the site at the clinic visits, where compliance was evaluated by counting unused tablets and capsules. The investigators, participants, clinical research organization, and sponsor of the trial were blinded to all lipid results from randomization until all participants had completed the final treatment visit.

Assessments

Fasting blood samples were collected at each clinic visit throughout the trial. Laboratory analyses were completed by Medpace Reference Laboratory (Cincinnati, OH). Lipid parameters (total cholesterol, high-density lipoprotein cholesterol [HDL-C], TG, non-HDL-C, Friedewald-calculated LDL-C, and very-low-density lipoprotein cholesterol [VLDL-C]) were measured using AU5800 analyzers (Beckman Coulter, Brea, CA), and apolipoprotein (Apo) B using the Antellica® NEPH 630 System/BNII System/ProSpec® system (Siemens Healthcare Diagnostics Products, Marburg, Germany). If a participant had a TG level ≥400 mg/dL or an LDL-C level ≤50 mg/dL, then LDL-C was measured by preparative ultracentrifugation (also known as beta-quantification). Centrifugation was performed at 40,000 rpm for 18–22 h at 10°C to separate VLDL and chylomicrons into the supernatant (<1.006 g/mL density) and LDL, intermediate-density lipoprotein (IDL), lipoprotein(a) [Lp(a)], and HDL into the infranatant. Apo B–containing lipoproteins were then precipitated from whole serum using 50 kDa dextran sulfate with Mg ions and cholesterol was measured in the remaining HDL fraction. Finally, HDL-C was subtracted from the infranatant cholesterol to

Table 1 Demographic and baseline characteristics in the on-treatment population.

Characteristic[1]	Placebo ($n = 40$)	Obicetrapib 10 mg ($n = 26$)	Obicetrapib 10 mg + Ezetimibe 10 mg ($n = 31$)
Age, y	60.6 ± 8.46	64.8 ± 7.24	63.5 ± 9.08
Sex, n (%)			
Male	26 (65.0)	17 (65.4)	19 (61.3)
Female[2]	14 (35.0)	9 (34.6)	12 (38.7)
Ethnicity, n (%)			
Hispanic or Latino	4 (10.0)	2 (7.7)	3 (9.7)
Not Hispanic or Latino	35 (87.5)	24 (92.3)	28 (90.3)
Not reported	1 (2.5)	0 (0.0)	0 (0.0)
Race, n (%)			
White	30 (75.0)	23 (88.5)	29 (93.5)
Black/African American	9 (22.5)	3 (11.5)	2 (6.5)
Asian	1 (2.5)	0 (0.0)	0 (0.0)
Body mass index, kg/m^2	30.8 ± 4.29	29.9 ± 4.61	31.8 ± 5.52
LDL-C category, n (%)			
<100 mg/dL	20 (50.0)	13 (50.0)	18 (58.1)
≥100 mg/dL	20 (50.0)	13 (50.0)	13 (41.9)
Current statin therapy, n (%)			
Atorvastatin	30 (75.0)	19 (73.1)	25 (80.6)
Rosuvastatin	10 (25.0)	8 (30.8)	6 (19.4)

[1]Values are mean ± standard deviation unless otherwise indicated.
[2]The placebo group included two women of childbearing potential.
Abbreviation: LDL-C, low-density lipoprotein cholesterol.

determine LDL-C. Thus, LDL-C measured by preparative ultracentrifugation includes the biological LDL-C fraction plus IDL-C and Lp(a)-C. For sensitivity analyses, LDL-C was also measured by preparative ultracentrifugation in all participants at baseline and week 12, and LDL-C was also calculated using the Martin/Hopkins equation, which is a modified version of the Friedewald equation that uses a novel factor based on the participant's non-HDL-C and TG values, instead of the fixed ratio of TG/5.[14] Nuclear magnetic resonance (NMR) spectra for LDL and HDL particles were acquired from serum samples on a Vantera® Clinical Analyzer (LabCorp, Morrisville, NC) as previously described.[15, 16] Small LDL particles were defined as those in the range of 18–21.2 nm, small HDL as 7.3–8.2 nm, medium HDL as 8.2–8.8 nm, and large HDL as 8.8–13 nm. PCSK9 was measured using Quantikine® ELISA (R&D Systems, Inc., Minneapolis, MN). Samples for measurement of plasma obicetrapib concentration were collected pre-dose at randomization and weeks 4 and 12, and at the safety follow-up visit (week 16). During the treatment period, the sampling time was at least 24 h since the last dose of study drug. Chemical analysis of obicetrapib was performed using liquid chromatography (Shimadzu LC-30 AD)/mass spectrometry (AB Sciex Triple Quad 5500 System).

Statistics

The primary endpoint was the percent change from baseline to week 12 in Friedewald-calculated LDL-C for the obicetrapib plus ezetimibe combination treatment group compared with placebo. Secondary efficacy endpoints included the percent changes from baseline to week 12 in LDL-C for obicetrapib monotherapy vs. placebo, and in Apo B for the obicetrapib plus ezetimibe combination vs. placebo and the obicetrapib monotherapy vs. placebo groups. Exploratory efficacy endpoints included percent changes from baseline to week 12 in non-HDL-C, VLDL-C, HDL-C, TG, NMR-assessed lipoprotein particles, PCSK9, and the proportion of participants at the end of treatment that achieved LDL-C levels below 100 mg/dL, 70 mg/dL, and 55 mg/dL for the obicetrapib combination and monotherapy groups compared with placebo.[17, 18]

A sample size of at least 108 evaluable participants (36 per treatment group) was determined to provide more than 90% power to detect a 30% difference in LDL-C reduction at week 12 (standard deviation of 15%) for each of the obicetrapib treatment groups compared to placebo at a two-sided significance level of 0.05. All statistical analyses were performed using SAS® version 9.4 (SAS Institute, Cary, NC). The pre-specified primary analysis population was the modified intent-to-treat (mITT) population, defined as all participants who received at least one dose of study drug and had a baseline value for LDL-C. Efficacy was also analyzed in the ITT population (all randomized participants) and in the per protocol (PP) population (all participants receiving at least one dose of study drug, with LDL-C measured at baseline and week 12, and with no major protocol deviation). The PK population for plasma obicetrapib analysis was defined as all participants in the mITT population who had sufficient blood samples collected for valid estimation

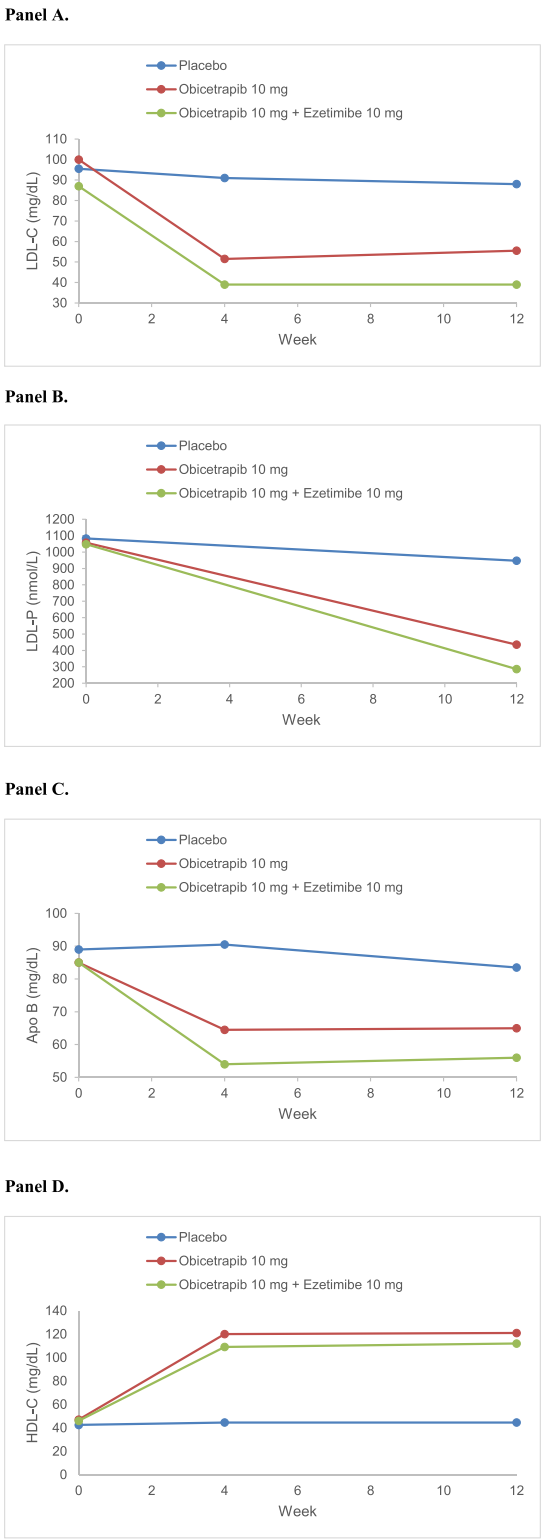

Figure 2 Median Friedewald-calculated LDL-C (Panel A), LDL-P (Panel B), Apo B (Panel C), and HDL-C (Panel D) for the placebo ($n = 40$), obicetrapib 10 mg ($n = 26$), and obicetrapib 10 mg + ezetimibe 10 mg treatment groups ($n = 31$) administered on a background of high-intensity statin treatment, in the on-treatment population at baseline and after 4 and 12 weeks of treatment. Abbreviations: Apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LDL-P, low-density lipoprotein particles

of PK parameters. The safety population was defined as all participants who received at least one dose of any study drug.

The analysis of the percent change from baseline to end of treatment in Friedewald-calculated LDL-C (the primary endpoint) was performed with a mixed model for repeated measures (MMRM) approach using SAS Proc Mixed. The analysis included fixed effects for treatment, visit, and treatment-by-visit interaction, and the baseline value as a continuous covariate. The restricted maximum likelihood estimation approach was used with an unstructured covariance matrix. Least squares (LS) means, standard errors (SE), and two-sided 95% confidence intervals for the obicetrapib plus ezetimibe combination group and for the comparison of the combination group to the placebo group were determined. The MMRM approach included all available assessments of percent change in LDL-C and assumed that data were missing at random. No imputation of missing data was performed for the primary efficacy endpoint analysis. Four sensitivity analyses were also performed for the primary endpoint including: MMRM with imputation, analysis of covariance (ANCOVA), ANCOVA using LDL-C by preparative ultracentrifugation only, and MMRM (no imputation) using LDL-C by the Martin/Hopkins calculation. Some non-normality was observed in the distribution of the residuals (significant Shapiro–Wilk tests) but was not sufficiently large to require transformations. For perspective, both LS mean (SE) and median (range limit) values are reported in the tables, and median values are emphasized in the text and figures.

Similar MMRM models as described for the primary endpoint were used to analyze the secondary and exploratory efficacy endpoints. To maintain the overall type 1 error rate, the secondary efficacy endpoints were tested sequentially at the 0.05 significance level (two-tailed) according to the hierarchy of the percent change from baseline to week 12 for: 1) LDL-C for obicetrapib monotherapy vs. placebo, 2) Apo B for obicetrapib plus ezetimibe combination therapy vs. placebo, and 3) Apo B for obicetrapib monotherapy vs. placebo. Logistic regression models using SAS Proc LOGISTIC with covariates of treatment group and baseline LDL-C value were used to examine the proportion of participants achieving LDL-C levels of <100 mg/dL, <70 mg/dL, and <55 mg/dL. No adjustments for multiplicity were made in testing the exploratory endpoints and nominal p-values were provided.

After the database was locked and reviewed, it was determined that an unusually large number of participants assigned to obicetrapib had very low or no detectable plasma levels of study drug at the end of the treatment period, despite indicating compliance by pill counts, suggesting that some level of participant misconduct was likely and therefore data from these participants are potentially suspect. Most of these participants were from two of the study sites. After discussion with the academic study leadership, an additional 'on-treatment' analysis excluded participants in the obicetrapib treatment groups with plasma obicetrapib concentrations <100 ng/mL (three standard deviations from the mean plasma obicetrapib concentration observed in prior studies

of obicetrapib) at either or both week 4 and week 12.[12, 13] In none of the previously conducted studies (three clinical studies and two multiple-ascending dose studies) was the minimal observed obicetrapib concentration below 100 ng/mL (Data on file, NewAmsterdam Pharma). In a similar situation with potential subject misconduct, regulatory agencies have supported the on-treatment analysis for phase 3 trials.[19] Additional sensitivity analyses were also completed in which data from the two sites with the largest number of subjects with very low or zero values for obicetrapib were excluded. A *post hoc* sensitivity analysis was also conducted to investigate the LDL-C response in the sample which excluded subjects with obicetrapib PK levels <200 µg/L (two standard deviations below the median of all previously conducted studies) to compare to a similar cohort in the previous Phase 2 Randomized Study of Obicetrapib as an Adjunct to High Intensity Statin Therapy (ROSE) trial.[13]

Results

Of the 119 subjects randomized, 97 (81.5%) were included in the on-treatment analysis. A summary of the participant flow throughout the trial is shown in Fig. 1. The results for the on-treatment population, which excluded subjects with suspected misconduct that occurred mainly at two sites, are presented in the manuscript, tables, and figures. Participants had a mean age of 62.6 years, 63.9% were male, 84.5% were white, and they had an average body mass index of 30.9 kg/m^2 (Table 1). All participants were treated with high-intensity statins; the majority were taking atorvastatin. Calculated compliance with tablets (placebo or obicetrapib) in the on-treatment population was 97.3%, 100%, and 99.2%, respectively, in the placebo, obicetrapib monotherapy, and obicetrapib combination treatment groups. Similarly, calculated compliance with capsules (placebo or ezetimibe) was 97.4%, 100%, and 98.9%, respectively.

Lipids, apo B, lipoprotein particles and PCSK9

Concentrations of lipids, Apo B, lipoprotein particles, and PCSK9 at baseline and during treatment, and percent changes from baseline to week 12 are presented in Tables 2 and 3, and Figs. 2, 3, 5, and Supplemental Figures 1 and 2. Friedewald-calculated LDL-C, the primary endpoint, was reduced from baseline by a median of 63.4% with obicetrapib and ezetimibe in combination, compared with a reduction of 43.5% with obicetrapib monotherapy and a 6.35% reduction with placebo (p<0.0001 vs. placebo for both). Results for LDL-C measured by the Friedewald calculation were comparable to those measured by preparative ultracentrifugation (−62.8%, −43.6%, and −3.95% for the obicetrapib plus ezetimibe combination, obicetrapib monotherapy, and placebo groups, respectively), and using the Martin/Hopkins equation (−64.7%, −42.1%, and −3.75%, respectively). All sensitivity analyses of LDL-C responses in the combination therapy group had similar findings. Achievement of LDL-C

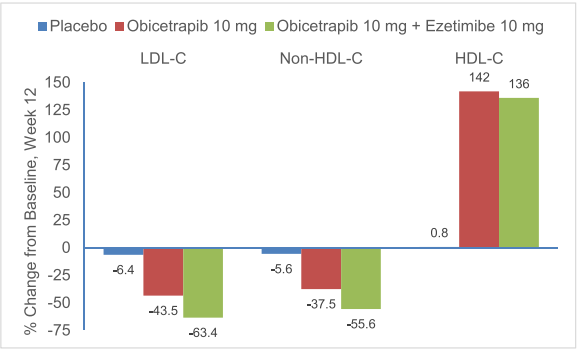

Figure 3 Median percent changes from baseline to the end of treatment (week 12) in LDL-C, non-HDL-C, and HDL-C for the placebo (n = 40), obicetrapib 10 mg (n = 26), and obicetrapib 10 mg + ezetimibe 10 mg treatment groups (n = 31) administered on a background of high-intensity statin treatment in the on-treatment population. Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol.

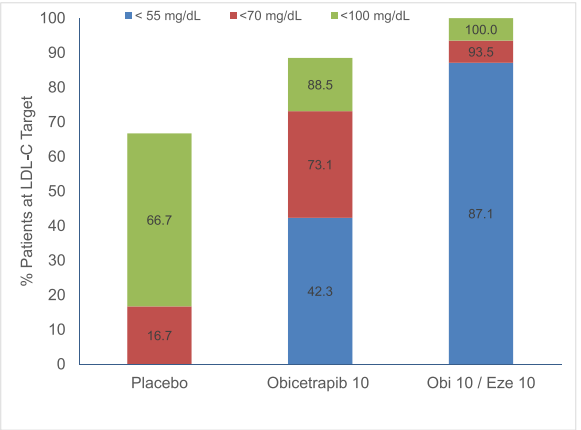

Figure 4 Achievement of LDL-C therapeutic objectives of <100, <70, and <55 mg/dL by participants in the placebo (n = 40), obicetrapib 10 mg (n = 26), and obicetrapib 10 mg + ezetimibe 10 mg treatment groups (n = 31) administered on a background of high-intensity statin treatment in the on-treatment population. Abbreviations: Eze, ezetimibe; LDL-C, low-density lipoprotein cholesterol; Obi, obicetrapib.

levels of <100, <70, and <55 mg/dL is shown in Fig. 4. Combination obicetrapib plus ezetimibe therapy resulted in significantly more subjects achieving each of these LDL-C levels than the placebo group (100%, 93.5%, and 87.1% vs. 66.7%, 16.7%, and 0.0%, respectively) (p<0.05 vs. placebo for all). The obicetrapib plus ezetimibe in combination and obicetrapib monotherapy treatments increased HDL-C by 136% and 142%, respectively (both p<0.0001 vs. placebo).

The obicetrapib plus ezetimibe in combination and obicetrapib monotherapy treatments reduced non-HDL-C by 55.6% and 37.5% and Apo B by 34.4% and 24.2%, respectively (all p<0.0001 vs. placebo). The NMR lipoprotein particle analysis demonstrated reductions in total LDL particles of 72.1% and 54.8% and small LDL particles of 95.4% and 92.7%, in the combination and obicetrapib monother-

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Table 2 Lipoprotein lipid and apo B concentrations at baseline and percent changes from baseline to week 12 in the on-treatment population.

Lipid and Time Point	Placebo ($n = 40$)[1]	Obicetrapib 10 mg ($n = 26$)	Obicetrapib 10 mg + Ezetimibe 10 mg ($n = 31$)
LDL-C (Friedewald-calculated)[2]			
Baseline, mg/dL			
Median (min, max)	95.5 (60, 211)	100 (35, 189)	87.0 (62, 152)
Week 12 change, %			
Median (min, max)	−6.35 (−36.4, 96.7)	−43.5 (−78.4, 22.6)	−63.4 (−83.7, −29.7)
LS mean ± SE	−0.85 ± 3.47	−39.2 ± 4.13	−59.2 ± 3.79
P-value vs. placebo		<0.0001	<0.0001
LDL-C (Preparative ultracentrifugation)[3]			
Baseline, mg/dL			
Median (min, max)	95.0 (59, 205)	102 (35, 191)	91.0 (64, 163)
Week 12 change, %			
Median (min, max)	−3.95 (−34.3, 91.8)	−43.6 (−78.4, 20.4)	−62.8 (−82.3, −31.0)
LS mean ± SE	−1.54 ± 3.53	−38.8 ± 4.17	−59.7 ± 3.81
P-value vs. placebo		<0.0001	<0.0001
LDL-C (Martin/Hopkins-calculated)[2]			
Baseline, mg/dL			
Median (min, max)	97.0 (59, 208)	102 (36, 187)	91.0 (61, 157)
Week 12 change, %			
Median (min, max)	−3.75 (−37.1, 100)	−42.1 (−65.0, 21.7)	−64.7 (−86.7, −30.9)
LS mean ± SE	−0.60 ± 3.41	−40.5 ± 4.06	−63.3 ± 3.72
P-value vs. placebo		<0.0001	<0.0001
Non-HDL-C[2]			
Baseline, mg/dL			
Median (min, max)	126 (73, 227)	122 (57, 209)	116 (77, 189)
Week 12 change, %			
Median (min, max)	−5.55 (−34.9, 83.6)	−37.5 (−59.2, 20.0)	−55.6 (−76.2, −30.8)
LS mean ± SE	−0.84 ± 2.99	−33.8 ± 3.55	−54.0 ± 3.25
P-value vs. placebo		<0.0001	<0.0001
Apo B[2]			
Baseline, mg/dL			
Median (min, max)	89.0 (52, 146)	85.0 (33, 130)	85.0 (56, 130)
Week 12 change, %			
Median (min, max)	−2.05 (−30.9, 76.9)	−24.2 (−44.8, 27.1)	−34.4 (−54.3, −14.7)
LS mean ± SE	0.72 ± 2.57	−21.6 ± 3.05	−35.0 ± 2.80
P-value vs. placebo		<0.0001	<0.0001
VLDL-C[2]			
Baseline, mg/dL			
Median (min, max)	22.0 (10, 72)	22.5 (15, 61)	25.0 (10, 58)
Week 12 change, %			
Median (min, max)	0.0 (−61.1, 93.8)	−2.95 (−59.0, 133)	−13.8 (−62.1, 168)
LS mean ± SE	−0.92 ± 6.32	3.36 ± 7.39	−4.94 ± 6.77
P-value vs. placebo		0.6614	0.6647
HDL-C[2]			
Baseline, mg/dL			
Median (min, max)	42.5 (31, 68)	47.0 (28, 111)	46.0 (28, 76)
Week 12 change, %			
Median (min, max)	0.75 (−33.3, 45.0)	142 (34.9, 311)	136 (46.5, 261)
LS mean ± SE	−0.32 ± 6.71	151 ± 8.15	144 ± 7.27
P-value vs. placebo		<0.0001	<0.0001
TG[2]			
Baseline, mg/dL			
Median (min, max)	111 (52, 362)	113 (73, 305)	126 (50, 289)

(*continued on next page*)

Table 2 (*continued*)

Lipid and Time Point	Placebo ($n = 40$)[1]	Obicetrapib 10 mg ($n = 26$)	Obicetrapib 10 mg + Ezetimibe 10 mg ($n = 31$)
Week 12 change, %			
Median (min, max)	−1.10 (−62.0, 91.3)	−4.30 (−59.0, 130)	−15.6 (−61.2, 170)
LS mean ± SE	0.95 ± 6.39	2.89 ± 7.57	−5.60 ± 6.92
P-value vs. placebo		0.8450	0.4891

[1]Numbers of subjects at baseline were as labeled for all analyses, and numbers of subjects for percent change analyses were as labeled for all analyses, except placebo for VLDL-C which was $n = 36$.

[2]Least squares mean ± SE and p-values are from a mixed model for repeated measured model which included fixed effects for treatment, visit, and treatment-by-visit interaction, along with a covariate of the baseline value as a continuous covariate. Missing at random was assumed for all missing data at scheduled visits.

[3]Least squares mean ± SE and p-values are from an analysis of covariance model with fixed effects treatment group and baseline value as a continuous covariate.

Abbreviations: Apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LS, least squares; SE, standard error; TG, triglycerides; VLDL-C, very low-density lipoprotein cholesterol.

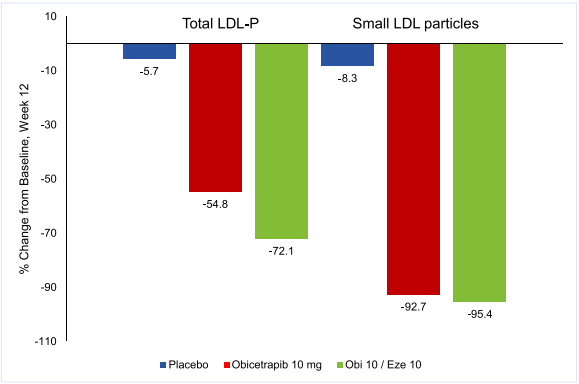

Figure 5 Median percent changes from baseline to the end of treatment (week 12) in the concentration of total LDL particles and small LDL particles for the placebo ($n = 34$), obicetrapib 10 mg ($n = 26$), and obicetrapib 10 mg + ezetimibe 10 mg treatment groups ($n = 31$) administered on a background of high-intensity statin treatment in the on-treatment population. Abbreviations: Eze, ezetimibe; LDL, low-density lipoprotein; LDL-P, low-density lipoprotein particles; Obi, obicetrapib.

apy treatments, respectively (all $p<0.0001$ vs. placebo), and increases in LDL particle size of 1.75% and 1.45%, large HDL particles of 197% and 146%, and HDL particle size of 19.8% and 19.3%, respectively (all $p<0.0001$ vs. placebo). Total HDL particle concentration was increased in the obicetrapib plus ezetimibe combination group (3.50%, $p<0.05$ vs. placebo), whereas the change in the obicetrapib monotherapy group (−0.05%) was not different from placebo. Small HDL particle concentration was reduced by 52.1% with obicetrapib monotherapy ($p<0.05$ vs. placebo), but the change in the obicetrapib plus ezetimibe combination group (−28.6%) was not different from placebo. There were no significant differences in the concentrations of VLDL-C, TG, medium HDL particles, or PCSK9 for either the combination therapy group or monotherapy treatment group compared with placebo.

Results for the mITT population were not materially different from those for the on-treatment population and are provided in the Supplementary Materials. Similarly, results for additional sensitivity analyses, including the analysis in which data from the two sites with the largest number of subjects with very low or zero values for obicetrapib were excluded, were not materially different from that of the mITT analysis population (data not shown). The *post hoc* sensitivity analysis that excluded subjects with obicetrapib PK levels <200 µg/L demonstrated a median LDL-C reduction of 47%.

Safety

Treatment-emergent adverse events were reported by 35 (29.4%) of the 119 participants in the safety population: 16 participants (40.0%) in the placebo group, 8 participants (20.5%) in the obicetrapib 10 mg group, and 11 participants (27.5%) in the combination obicetrapib plus ezetimibe group. Adverse events reported by at least two participants in any treatment group are shown in Table 4. The most prevalent adverse events were nausea, urinary tract infection, and headache. Most events were classified as mild or moderate in severity. Five participants discontinued the study due to adverse events: 2 (5.0%) in the placebo group, 2 (5.1%) in the obicetrapib 10 mg group, and 1 (2.5%) in the combination obicetrapib plus ezetimibe group. There were no clinically meaningful changes in biochemical safety measures or vital signs in either obicetrapib group compared with placebo. An analysis of adverse events in the on-treatment population indicated no material differences from the analysis of the safety population.

Obicetrapib concentrations

Median plasma obicetrapib concentrations at week 4 in the obicetrapib 10 mg and combination obicetrapib 10 mg plus ezetimibe 10 mg treatment groups of the on-treatment population were 387 and 348 µg/L, respectively, and remained steady at week 12 (levels were 387 and 360 µg/L, respectively). At the visit four weeks following end of treat-

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Table 3 Lipoprotein particle and PCSK9 concentrations at baseline and percent changes from baseline to week 12 in the on-treatment population.

Lipid and Time Point	Placebo ($n = 40$)[1]	Obicetrapib 10 mg ($n = 26$)	Obicetrapib 10 mg + Ezetimibe 10 mg ($n = 31$)
Total LDL particles[2]			
Baseline, nmol/L			
Median (min, max)	1083 (632, 1650)	1057 (275, 1588)	1048 (692, 1848)
Week 12 change, %			
Median (min, max)	−5.65 (−38.6, 35.9)	−54.8 (−82.4, 4.7)	−72.1 (−95.7, −12.9)
LS mean ± SE	−6.65 ± 3.09	−53.8 ± 3.54	−69.9 ± 3.24
P-value vs. placebo		<0.0001	<0.0001
Small LDL particles[2]			
Baseline, nmol/L			
Median (min, max)	717 (316, 1088)	702 (84, 1517)	763 (68, 1411)
Week 12 change, %			
Median (min, max)	−8.30 (−36.7, 86.2)	−92.7 (−98.3, 11.9)	−95.4 (−99.8, 1.5)
LS mean ± SE	−3.22 ± 3.53	−86.5 ± 4.05	−89.1 ± 3.70
P-value vs. placebo		<0.0001	<0.0001
LDL particle size[2]			
Baseline, nm			
Median (min, max)	20.3 (19.6, 21.6)	20.6 (19.6, 21.6)	20.1 (19.6, 21.8)
Week 12 change, %			
Median (min, max)	−0.50 (−5.6, 4.1)	1.45 (−2.8, 5.6)	1.75 (−4.6, 5.5)
LS mean ± SE	−0.88 ± 0.30	2.44 ± 0.44	2.36 ± 0.70
P-value vs. placebo		<0.0001	0.0001
Total HDL particles[2]			
Baseline, nmol/L			
Median (min, max)	32.4 (23.3, 41.7)	35.2 (25.0, 48.7)	35.3 (24.1, 41.6)
Week 12 change, %			
Median (min, max)	−0.20 (−31.7, 22.5)	−0.05 (−35.7, 38.8)	3.50 (−30.4, 46.9)
LS mean ± SE	−5.66 ± 2.38	1.22 ± 2.72	5.97 ± 2.46
P-value vs. placebo		0.0638	0.0010
Large HDL particles[2]			
Baseline, nmol/L			
Median (min, max)	6.10 (2.1, 10.6)	7.45 (1.3, 19.7)	6.10 (0.7, 14.1)
Week 12 change, %			
Median (min, max)	3.55 (−45.7, 70.2)	146 (3.6, 1415)	197 (61, 1300)
LS mean ± SE	−18.0 ± 30.0	264 ± 34.7	276 ± 31.2
P-value vs. placebo		<0.0001	<0.0001
Medium HDL particles[2]			
Baseline, nmol/L			
Median (min, max)	8.10 (0.5, 22.4)	9.90 (0.0, 34.4)	6.70 (0.9, 27.8)
Week 12 change, %			
Median (min, max)	3.40 (−71.3, 860)	−46.5 (−100, 161)	−52.6 (−100, 1500)
LS mean ± SE	39.3 ± 32.4	−16.3 ± 38.6	−1.48 ± 34.3
P-value vs. placebo		0.2742	0.3897
Small HDL particles[2]			
Baseline, nmol/L			
Median (min, max)	17.4 (0.0, 33.2)	18.1 (2.1, 30.3)	19.0 (0.9, 32.7)
Week 12 change, %			
Median (min, max)	−6.50 (−54.4, 69.6)	−52.1 (−100, 35.5)	−28.6 (−100, 656)
LS mean ± SE	−10.6 ± 12.9	−51.6 ± 14.6	−7.25 ± 13.4
P-value vs. placebo		0.0375	0.8590

(*continued on next page*)

Table 3 (*continued*)

Lipid and Time Point	Placebo ($n = 40$)[1]	Obicetrapib 10 mg ($n = 26$)	Obicetrapib 10 mg + Ezetimibe 10 mg ($n = 31$)
HDL particle size[2]			
Baseline, nm			
Median (min, max)	9.20 (8.4, 10.2)	9.35 (8.6, 10.5)	9.10 (8.4, 10.3)
Week 12 change, %			
Median (min, max)	0.00 (−5.1, 9.1)	19.3 (12.4, 26.7)	19.8 (9.7, 27.3)
LS mean ± SE	0.65 ± 0.56	19.7 ± 0.64	19.2 ± 0.59
P-value vs. placebo		<0.0001	<0.0001
PCSK9[2]			
Baseline			
Median (min, max)	371 (201, 612)	413 (220, 693)	391 (275, 659)
Week 12 change, %			
Median (min, max)	0.25 (−27.2, 53.3)	1.80 (−36.5, 45.2)	4.40 (−27.3, 63.9)
LS mean ± SE	4.02 ± 3.18	4.06 ± 3.74	5.69 ± 3.43
P-value vs. placebo		0.9928	0.7212

[1]Numbers of subjects at baseline were as labeled except LDL and HDL particle concentrations for which placebo was $n = 39$. Numbers of subjects for percent change analyses were as labeled except placebo for all LDL and HDL particle concentrations and size which were $n = 34$ for placebo and small HDL particle concentration which was $n = 33$ for placebo.

[2]Least squares mean ± SE and p-values are from an analysis of covariance model with fixed effects treatment group and baseline value as a continuous covariate.

Abbreviations: HDL, high-density lipoprotein; LS, least squares; PCSK9, proprotein convertase subtilisin kexin type 9; SE, standard error.

Table 4 Treatment-emergent adverse events occurring in at least two subjects for any treatment condition in the safety population.

System organ class Preferred term[1]	Placebo ($n = 40$)	Obicetrapib 10 mg ($n = 39$)	Obicetrapib 10 mg + Ezetimibe 10 mg ($n = 40$)
		n (%)	
Infections and infestations	5 (12.5)	1 (2.6)	4 (10.0)
Urinary tract infection	2 (5.0)	0 (0.0)	1 (2.5)
Gastrointestinal disorders	2 (5.0)	2 (5.1)	4 (10.0)
Nausea	2 (5.0)	0 (0.0)	2 (5.0)
Injury, poisoning and procedural complications	1 (2.5)	3 (7.7)	4 (10.0)
Nervous system disorders	4 (10.0)	3 (7.7)	0 (0.0)
Headache	2 (5.0)	1 (2.6)	0 (0.0)
Investigations[2]	3 (7.5)	1 (2.6)	1 (2.5)
Musculoskeletal and connective tissue disorders	3 (7.5)	0 (0.0)	1 (2.5)
Myalgia	2 (5.0)	0 (0.0)	0 (0.0)
Cardiac disorders	0 (0.0)	3 (7.7)	0 (0.0)

[1]Terms were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 24.1.

[2]The MedDRA system organ class defined as laboratory tests and other medical investigations that gave an unusual reading.

ment, obicetrapib levels had decreased to 17.8 and 27.1 μg/L, respectively.

Discussion

In this trial in people with elevated LDL-C while receiving high-intensity statin therapy, the combination of obicetrapib and ezetimibe significantly reduced LDL-C by 63.4%, non-HDL-C by 55.6%, Apo B by 34.4%, and the concentrations of total and small LDL particles by 72% and 95%, respectively. Monotherapy with obicetrapib also significantly reduced LDL-C by 44%. In five clinical trials, 10 mg obicetrapib reduced LDL-C by 44 to 51%, confirming consistent efficacy either in combination with high-intensity statins or as monotherapy (Data on file, NewAmsterdam Pharma).[11-13] In consideration of potential compliance difference between ROSE and ROSE2, we conducted a *post hoc* analysis comparing LDL-C–lowering efficacy in the two trials in the cohorts which excluded patients with obicetrapib PK levels <200 μg/L (two standard deviations below the median of all

previously conducted studies). In this sensitivity analysis, the median LDL-C lowering in ROSE vs. ROSE2 was 51% vs. 47%, respectively, also confirming consistent efficacy for obicetrapib in combination with high-intensity statins. The extent of atherogenic lipoprotein lowering in the obicetrapib plus ezetimibe treatment group in ROSE2 supports at least an additive effect of obicetrapib and ezetimibe on top of statin, which is consistent with the different mechanisms of action of obicetrapib, a CETP inhibitor, ezetimibe, a Niemann-Pick C1-Like 1 inhibitor, and statins, which inhibit 3–hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase.[20-22] In addition to impairing the transfer of cholesteryl esters from HDL to Apo B–containing particles, CETP inhibition may also increase transintestinal cholesterol excretion, contributing to fecal sterol excretion, and upregulate scavenger receptor class B type I and hepatic LDL receptor expression, all of which result in lower plasma LDL-C[22-24] (Supplementary Figure 3). The large majority of participants receiving the combination of obicetrapib and ezetimibe in ROSE2 reached LDL-C levels of <100 mg/dL, <70 mg/dL, and even the most aggressive therapeutic objective of <55 mg/dL,[17, 18] which was achieved by 87.1% of high-intensity statin-treated participants receiving combination therapy compared with 42.3% of participants receiving obicetrapib monotherapy and no persons taking placebo.

Considerable evidence suggests that any cardioprotective effect of reductions in CETP are likely to be related to reductions in Apo B–containing lipoproteins. Mendelian randomization studies demonstrate that reductions in cardiovascular risk associated with low CETP activity are directly related to lower levels of Apo B.[25] The only cardiovascular outcome trial demonstrating clinical benefit with a CETP inhibitor, using anacetrapib,[26] suggested the benefit was related to its effects on LDL-C, non-HDL-C, and Apo B, in contrast to the original belief that raising HDL-C with CETP inhibition was the driver of reduced ASCVD risk.[25] The finding of additional reduction in major coronary events (a further 20%) on longer follow-up after the 4-year trial further supported the effects of lowering atherogenic lipid parameters.[26, 27] However, the clinical development of anacetrapib was halted after a positive cardiovascular outcome trial, because of the finding that it accumulated in adipose tissue.[28] In this study, plasma concentrations of obicetrapib decreased substantially after the end of treatment and there is no indication of tissue accumulation. Based on results from phase 1 PK studies of obicetrapib, its terminal half-life is between 121 and 151 h at 1- to 25-mg doses.[11] Cardiovascular outcomes trials of other CETP inhibitors all failed to demonstrate clinical benefit, but these failures were due to compound-specific issues including off-target adverse effects with torcetrapib,[29] insufficient LDL-C lowering with dalcetrapib,[30] and insufficient follow-up duration for the amount of LDL-C lowering produced by evacetrapib.[31]

The findings of this study have potentially important implications for the prevention of ASCVD events. The addition of ezetimibe to obicetrapib extends previous reports of the effect of obicetrapib monotherapy on atherogenic lipid and lipoprotein parameters in high-intensity statin–treated patients to achieve an even greater effect on biochemical factors associated with cardiovascular risk. The ability to reduce LDL-C by 63%, Apo B by 34%, total LDL particles by 72%, and small LDL particles by 95% would be predicted to produce further reductions in the risk of cardiovascular events in patients treated with high-intensity statins. The ongoing Cardiovascular Outcomes Study to Evaluate the Effect of Obicetrapib in Patients with Cardiovascular Disease (PREVAIL; NCT05202509) will examine whether decreasing atherogenic particles with obicetrapib reduces ASCVD risk. PREVAIL is enrolling 9000 patients and is targeted for completion late in 2026. In addition, these findings suggest that the combination of obicetrapib and ezetimibe can produce more effective reductions in lipid parameters than the combination of bempedoic acid and ezetimibe and is at least comparable to the effects of PCSK9 inhibitors, without the need for injections.

The effects on HDL parameters are also of potential interest. HDL-C increased by approximately 150% with obicetrapib and ezetimibe, primarily related to an increase in larger HDL particles. Larger HDL particles contain more cholesterol and are subsequently cleared primarily through the liver by the scavenger receptor class B type I pathway,[32, 33] in contrast to pre-beta-1 HDL particles which mediate cholesterol efflux via the ATP-binding cassette transporter A1 (ABCA1). Prior studies, which measured HDL particle distribution using two-dimensional gel electrophoresis, demonstrated increases in pre-beta-1 HDL of 36% and pre-beta-2 HDL of 66% among patients taking obicetrapib monotherapy.[34] Furthermore, the increase in pre-beta-1 HDL correlated with total and ABCA1-driven cholesterol efflux capacity. These results suggest that obicetrapib increases cholesterol flux through the HDL fraction. Additional studies are needed to further understand the effects of obicetrapib on HDL particle subfractions and the roles these changes might play not only in cardiovascular disease but also in Alzheimer's disease, diabetes mellitus, sepsis, and age-related macular degeneration.[35, 36]

It is also important to note the assay-independent nature of the LDL-C response to obicetrapib. A previous analysis reported differences between LDL-C values measured directly compared with those determined using preparative ultracentrifugation in patients taking anacetrapib.[37] However, the results from both ROSE and ROSE2 indicated comparable LDL-C values with obicetrapib treatment measured by using the Friedewald equation, preparative ultracentrifugation, and the Martin/Hopkins equation.[13] Obicetrapib, administered as monotherapy or in combination with ezetimibe was well tolerated when added to background high-intensity statin therapy, consistent with expectations based on previous trials of both obicetrapib and ezetimibe.[11-13, 38, 39]

A few potential limitations require additional comment. The sample size was small and the treatment period was short, given the objective was to evaluate the impact on lipid and lipoprotein changes, not cardiovascular outcomes. Ongoing trials will determine the longer-term effects on

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both lipid parameters and clinical events (NCT05202509, NCT05142722, and NCT05425745). The study did not include an ezetimibe monotherapy group, although its lipid effects are well established. A number of analyses are included in both the manuscript and supplementary material, given the finding that nearly 20% of patients treated with obicetrapib had either no or low discernible blood concentrations on PK evaluation. While it is reassuring that similar findings were observed in each of these analyses, given the objective of the study was to evaluate the effect of combination therapy with obicetrapib and ezetimibe on lipid parameters, the academic leadership determined it was important to perform an analysis excluding patients in which there was a concern regarding the integrity of their data.

In conclusion, this study demonstrated the efficacy of obicetrapib in combination with ezetimibe as an adjunct to high-intensity statin for producing robust reductions in LDL-C, non-HDL-C, Apo B, and total and small LDL particle concentrations, while increasing HDL-C compared with high-intensity statin monotherapy. This supports the development of a fixed dose combination of obicetrapib plus ezetimibe and further shows the potential of obicetrapib to be the first CETP inhibitor to advance to clinical practice and fill the treatment gap for patients unable to achieve adequate LDL-C reductions with other available lipid-lowering medications.

Disclosures

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Christie M. Ballantyne: Conceptualization, Writing – review & editing. **Marc Ditmarsch:** Conceptualization, Visualization, Writing – original draft, Writing – review & editing. **John JP Kastelein:** Conceptualization, Writing – original draft, Writing – review & editing. **Adam J. Nelson:** Writing – review & editing. **Douglas Kling:** Conceptualization, Project administration, Writing – review & editing. **Andrew Hsieh:** Conceptualization, Writing – review & editing. **Danielle L. Curcio:** Project administration. **Kevin C. Maki:** Writing – review & editing. **Michael H. Davidson:** Conceptualization, Writing – review & editing. **Stephen J. Nicholls:** Conceptualization, Writing – review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jacl.2023.05.098.

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